

**Stony Brook University  
The Graduate School**

Doctoral Defense Announcement

**Abstract**

Interactions Between *Francisella tularensis* and  
Cells of Innate Immunity

By

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*Francisella tularensis*, the causative agent of tularemia, is a highly virulent pathogen capable of infecting humans and many other different species. Most laboratory work carried out on this organism uses a live vaccine strain (LVS), which is lethal in mice but attenuated in humans, or a fully virulent strain known as Schu S4. Endothelial cells play a key role in the host response to pathogens by recruiting circulating leukocytes to areas of infection. *F. tularensis* exploits this process by replicating in recruited macrophages. To further explore this relationship, the interactions between *F. tularensis* and host cells of innate immunity were studied. The LVS upregulated proinflammatory mediators in human umbilical vein endothelial cells (HUVEC) and human monocyte-derived macrophages (huMDM). Live and killed LVS organisms elicited different patterns of adhesion molecule expression and cytokine secretion, a phenomenon not observed with huMDM. Murine bone marrow-derived macrophages produced little to no pro-inflammatory mediators when treated with the LVS. Nonetheless, the LVS replicated well in both types of macrophages. LpnA, a conserved lipoprotein of *Francisella*, was viewed as a candidate mediator of inflammation and virulence. However, LVS organisms lacking LpnA had no detectable phenotype. In contrast, recombinant LpnA stimulated huMDM and HUVEC, suggesting that it and other *Francisella* lipoproteins are potentially important in the pathogenesis of tularemia.

Because a dogma among *Francisella* researchers is that the bacteria reside primarily intracellularly in the blood of mammalian hosts, it was difficult to envision a scenario in which *F. tularensis* and its proinflammatory components could elicit responses in cell types other than phagocytes. Interestingly, in almost all cases, the majority of *F. tularensis* that were recovered from the blood of infected mice was in plasma rather than leukocytes. This distribution was observed irrespective of size of inoculum, route of inoculation, time post-inoculation, or virulence of the infecting strain. Together, these data make more clear the poorly understood pathogenesis of tularemia. The existence of an extracellular phase *in vivo* allows for *F. tularensis* or its lipoproteins to interact with multiple cells of innate immunity as disease progresses.

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